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CUTANEOUS TOXICITY EVALUATION OF AIR FORCE DEVELOPMENT MATERIALS - IV

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APRIL 1961

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AEROSPACE MEDICAL LABORATORY
AERONAUTICAL SYSTEMS DIVISION
AIR FORCE SYSTEMS COMMAND
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FOREWORD

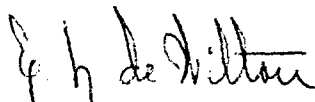
This report was initiated by the Toxic Hazards Section, Physiology Branch, Biomedical Laboratory, Aerospace Medical Laboratory, of the Aeronautical Systems Division, Wright-Patterson Air Force Base, Ohio. The contract monitor was Captain Alan B. Cooper, USAF, MC. The original research and development work upon which the report is based was accomplished by Industrial Biology Research and Testing Laboratories, Inc., 22 N. 36th Street, Philadelphia 4, Pennsylvania, under Air Force Contract No. AF 33(616)-6962, in support of Project No. 7165, "Health Hazards of Air Force Materials," Task No. 71836, "Toxicity of Air Force Materials." The author, Dr. Morris V. Shelanski, was project director in charge of the basic research and development work. Dr. Karl L. Gabriel was the assistant project director in charge of the work. Research was begun in February 1960 and completed in January 1961. Mr. Louis Shelanski, Animal Physiologist, and Dr. Theodore Levenson, Chemist, cooperated in the research and the preparation of the report.

The animal experimentation reported herein was performed according to the "Rules Regarding Animal Care" as approved by the American Medical Association.

ABSTRACT

Twelve Air Force development materials were studied via the prophetic patch test method on laboratory animals and volunteer human subjects to determine the primary irritant effect and the sensitization index of these materials. These materials were also studied by the Shelanski repeated insult patch test method on human volunteers to determine the primary irritation effect, fatiguing effect, and sensitization index. The patch test studies with rabbits indicated that only one material, Alkyldecalin, was too severe a primary irritant to test on humans. Upon testing the remaining materials on humans, Diethylcyclohexane was found to be a severe primary irritant. All other materials were found to be safe to use in contact with the human skin.

PUBLICATION REVIEW



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INTRODUCTION

Industrial Biology Research and Testing Laboratories, Inc., was engaged by the United States Air Force to perform dermatological studies and provide cutaneous toxicity data on certain Air Force development materials. These data would serve the Air Force as criteria for establishing safe handling procedures and limits of application of these materials when utilized by Air Force personnel.

There are various methods used for the determination of cutaneous toxicity of a chemical compound or substance. Laboratory animals, such as rabbits or guinea pigs, have been used by many investigators (ref. 5). The true index of cutaneous reaction can, however, only be determined by using human subjects. Prophetic patch tests are one of the methods used for this purpose (ref. 6 & 7). This test method helps to establish both the primary irritation and sensitization characteristics of a compound brought into contact with the human skin. Prophetic patch test studies were performed on laboratory animals and volunteer human subjects, to establish the primary irritant and sensitization characteristics of certain Air Force development materials including specifically chemically impregnated fabrics. The Shelanski repeated insult patch test (ref. 7), in addition to giving information about primary irritation and sensitization characteristics of the compound, will also bring out any fatiguing reactions which may occur on continuous contact of the material with the human skin. This technique was also performed on volunteer human subjects to more fully define the characteristics of these compounds on the skin of humans.

MATERIALS

The following materials were received from the Aerospace Medical Laboratory:

1. WF-151 - Di-2-ethylhexylsebacate
2. WF-213 - Bis (m-phenoxyphenol) ether
3. WF-236 - m-Bis (m-phenoxy phenoxy) benzene
4. WF-239 - Alkyldecalin
5. WF-240 - Diethylcyclohexane
6. WF-244 - Boron nitride
7. WF-248 - Ester of Trimethylolpropane
8. WF-251 - Contaminated Oronite Fluid 8515
9. WF-253 - Aircraft Grease
10. WF-254 - Hydrotherm 700-B
11. WF-255 - 3% Ammonium Hydroxide
12. WF-256 - Halon 1211 - Bromochlorodifluoromethane

CRITERIA FOR GRADING PATCH TEST REACTIONS

The investigators have discussed the criteria for grading patch test reactions used by various authors in a previous report, March, 1955 (ref. 3). In this study, as in the previous, the following criteria were used by the Industrial Biology Research and Testing Laboratories, Inc.

- 0 - no reaction, or questionable reaction
- 1+ - definite or clear-cut erythema
- 2+ - marked erythema, greater than present in 1+ reaction
- 3+ - marked erythema, edema, with or without a few vesicles
- 4+ - marked erythema, edema, with vesicles and oozing

RABBIT SCREENING STUDIES PROCEDURE

Twelve groups of five albino rabbits each were used in this study. The animals selected weighed approximately two kilograms each. Prior to use, the animals were placed on colony diet and observed for a period of two weeks. Animals not showing normal weight gain were replaced.

Prior to patching, the fur on the back of each rabbit was closely clipped to expose an area of skin equal to at least 10% of the total body area. This area was then shaved to denude the skin completely. The patch site area was marked with permanent ink to identify the site for later reference.

The test materials were applied to the denuded skin, covered with glassine paper, and held in place by means of a muslin binder. Approximately four grams of each material was spread over the exposed area of skin for each application. Five rabbits per material were used. The first or primary application remained in contact with the denuded skin for forty-eight hours. Upon removal, reactions were graded and recorded. Twenty-four hours after removal of the patches, the sites were examined for delayed reactions.

Following the primary application, the animals were rested for fourteen days. The patch material was then reapplied on the same site as a challenge or sensitization application. Again, after forty-eight hours contact, the patches were removed and reactions graded and recorded. Twenty-four hours later, the sites were examined for delayed reactions.

RESULTS AND CONCLUSIONS

Of the 12 materials, WF-239 was the only severe primary irritant on rabbits. After the primary application, one rabbit showed a 1+ reaction, one showed a 2+, and three showed a 3+. After the challenge application, two rabbits showed a 2+ reaction and three showed a 3+.

All the samples except WF-239 were considered safe for use in conducting patch tests on human subjects. After careful consideration, it was decided to include WF-239 in the first Schwartz patch test group of 50 human subjects, using extreme caution in the procedure.

HUMAN PATCH TESTS

SCHWARTZ PATCH TEST

PROCEDURE

Groups of normal, healthy, male volunteer subjects, aged 18-35, were used in this study. Each material was first tested on a group of 50 subjects.

The experimental materials were applied directly to the skin of the back and covered with a lintine disc. Approximately 2 grams of each material was used per subject. All patches were protected by glassine paper and held in place with one-half inch adhesive tape. Two applications were made in accordance with the Schwartz Patch Test Method: the first application to determine primary irritation and the second or challenge application to determine possible sensitization. The primary application remained in contact with the skin for forty-eight hours. Upon removal all reactions were graded and recorded. Seventy-two and ninety-six hours later, the sites were examined for delayed reactions.

Following removal of the primary application, the subjects were rested for two weeks. The second or challenge application was then applied. This patch also remained in contact with the skin for forty-eight hours. Upon removal, reactions were graded and recorded. Seventy-two and ninety-six hours later, the sites were examined for delayed reactions.

RESULTS FOR 50 SUBJECTS

Ten of the materials tested on the first 50 human subjects caused no reactions after the primary and challenge applications. Two of the materials, WF-239 and WF-240, proved to be severe irritants and, during the second day of the primary application, the patches were removed. These materials were not used for further testing.

Detailed results of the two irritants were:

WF-239 - Three subjects showed no reaction, five showed a 1+, ten showed a 2+, twenty-two showed a 3+, and ten showed a 4+.

WF-240 - Five subjects showed no reaction, three showed a 1+, thirteen showed a 2+, twenty-two showed a 3+, and seven showed a 4+.

FURTHER TEST PROCEDURE AND RESULTS

All the materials except WF-239 and WF-240 were tested in the same manner on additional groups of 250 subjects. None of the subjects reacted after either the primary or challenge applications.

No delayed reactions were noted during the follow-ups: 24, 48, 72, and 96 hours after application.

SHELANSKI REPEATED INSULT PATCH TEST

PROCEDURE

All the materials except WF-239 and WF-240 were tested on 300 human subjects, using the Shelanski repeated insult patch test method (ref. 7).

Not more than five test materials and necessary controls were tested on a single individual. The sample was applied with the conventional patch technique to the skin of the subjects for twenty-four hours and then removed. Skin reactions were graded and recorded. The skin was allowed to recuperate for twenty-four hours. This cycle of contact and recuperation was repeated fifteen times for a total of thirty days, the reaction being graded after each application. Following the removal and the grading of the fifteenth application the skin was allowed to recuperate for two weeks. The material was then re-applied on the same subjects for twenty-four hours. Patches then were removed and the reactions were graded and recorded. The first application gave an index of primary irritations. This final application gave information on sensitization. The repeated applications, from the second through the fifteenth, determined the extent of fatiguing and served to accelerate skin reactions which facilitated forecasting of probability of cutaneous irritation due to long-term exposures.

RESULTS

The ten materials caused no reactions during any of the applications. No delayed reactions were noted during the follow-ups: 24, 48, 72, and 96 hours after the challenge applications.

CONCLUSIONS

While all the interpretations and recommendations have been made on the basis of a generally accepted testing procedure, it must be pointed out that the test method is not infallible or above criticism. Further, the patch test situation does not duplicate the range of temperature, humidity, air flow, perspiration, and friction, among other factors, which will be met in actual usage of the material. Because the prophetic patch test was devised to provide screening information with respect to cutaneous irritation and sensitivity from certain materials, it must be emphasized that the test should be used only for that purpose. Therefore, the recommended procedure following the test is to employ the materials within the limits recommended for direct skin contact on a usage basis. This should be done on 5,000 to 10,000 subjects, preferably under variable climatic conditions prior to the release of the materials for general use.

The materials tested in this report were tested under two different human testing procedures. This denotes a departure from the past years in which only one human testing procedure was used, namely, the Schwartz method. The present materials were also subjected to a repeated insult patch test method devised by Shelanski and Shelanski. The latter method is designed not only to evaluate primary irritation and gross sensitization but also subtle sensitization and fatiguing agents. It has been the investigator's experience in the past that materials meeting the requirements of the Schwartz technique do not necessarily satisfy the requirements of the repeated insult patch test technique.

In this study, ten materials, namely, WF-151, WF-213, WF-236, WF-244, WF-248, WF-251, WF-253, WF-254, WF-255, and WF-256, produced no significant reactions by either the Schwartz prophetic test or the Shelanski repeated insult patch test technique. These ten materials are neither primary irritants, fatiguing agents, nor skin sensitizers. They are innocuous and may be permitted to contact the skin for prolonged periods.

WF-239, Alkyldecalin, is a severe primary irritant on rabbits and humans. It should be used with extreme caution where there is possibility of human skin contact. Personnel handling this material should use protective measures.

WF-240, Diethylcyclohexane, is a severe primary irritant on humans but not on rabbits. These results are contrary to those generally anticipated as rabbit skin is considered more delicate and more susceptible to primary irritation. WF-240 should be used with extreme caution where there is possibility of human skin contact. Personnel handling this material should use protective measures.

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